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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,710	09/04/2002	Atsuhiko Shinmyo	5404-18	4595

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EXAMINER	
COLLINS, CYNTHIA E	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 03/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,710	SHINMYO ET AL.	
	Examiner	Art Unit	
	Cynthia Collins	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *28-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *September 4, 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0602*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-27, in the reply filed on November 26, 2004 is acknowledged. Claims 28-37 are withdrawn as being directed to nonelected inventions.

Information Disclosure Statement

An initialed and dated copy of Applicant's IDS form 1449, filed June 21, 2002 is attached to the instant Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of inducing gene expression in a plant, and plants and plant cells made by said method. The claimed method requires that a plant be provided by gene transfer with a gene inducing system that comprises an operator and a repressor wherein an

actinomycete autogenous regulatory factor acts to induce the expression of a gene placed under the control of the operator.

The specification (pages 18-42) describes methods in which a plant is provided by gene transfer with a gene inducing system that comprises a first genetic construct comprising a GUS reporter gene placed under the control of a nucleotide sequence (SEQ ID NO:3) obtained from the barA gene of *Streptomyces virginiae* that functions as an operator and a second genetic construct comprising a nucleotide sequence (SEQ ID NO:1) obtained from the barA gene of *Streptomyces virginiae* that encodes a polypeptide (SEQ ID NO:2) that functions as a repressor wherein the actinomycete autogenous regulatory factor virginiae butanolide acts to induce the expression of a gene placed under the control of the operator sequence. The specification further describes the first genetic construct as comprising a cis-acting nucleotide sequence of SEQ ID NO:3 that functions as an operator when one, two or three copies of SEQ ID NO:3 are located 3' downstream and/or 5' upstream of the TATA box of the CaMV 35S promoter in the arrangement set forth in SEQ ID NOS: 4-7.

The specification does not describe other gene inducing systems that comprise other operator sequences and other repressor polypeptides wherein other types of actinomycete autogenous regulatory factors act to induce the expression of a gene placed under the control of the operator sequence. The specification also does not describe other arrangements of SEQ ID NO:3 that function as an operator when located 3' downstream and/or 5' upstream of the TATA box of the CaMV 35S promoter.

The Federal Circuit has recently clarified the application of the written description requirement as it applies to DNA sequences. The court stated that "A description of a genus of

cDNAs may be achieved by means of recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." See *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1569; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

In the instant case Applicant has not described a representative number of species falling within the scope of the claimed genus which encompasses gene inducing systems that comprise any operator sequence obtained from any source and any repressor polypeptide obtained from any source wherein any type of actinomycete autogenous regulatory factor may act to induce the expression of a gene placed under the control of the operator sequence, nor the structural features unique to the genus.

Claims 1-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a gene inducing system that comprises a first genetic construct comprising a GUS reporter gene placed under the control of a nucleotide sequence (SEQ ID NO:3) obtained from the barA gene of *Streptomyces virginiae* that functions as an operator when one, two or three copies of SEQ ID NO:3 are located 3' downstream and/or 5' upstream of the TATA box of the CaMV 35S promoter in the arrangement set forth in SEQ ID NOS: 4-7 and a second genetic construct comprising a nucleotide sequence (SEQ ID NO:1) obtained from the barA gene of *Streptomyces virginiae* that encodes a polypeptide (SEQ ID NO:2) that functions as a repressor wherein the actinomycete autogenous regulatory factor virginiae butanolide acts to induce the expression of a gene placed under the control of the operator sequence, does not

reasonably provide enablement for other gene inducing systems that comprise other operator sequences and other repressor polypeptides wherein other types of actinomycete autogenous regulatory factors act to induce the expression of a gene placed under the control of the operator sequence, or for other arrangements of SEQ ID NO:3 that function as an operator when located 3' downstream and/or 5' upstream of the TATA box of the CaMV 35S promoter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly drawn to a method of inducing gene expression in a plant, and plants and plant cells made by said method, including methods that require that a plant be provided by gene transfer with a gene inducing system that comprises any unspecified operator sequence and any unspecified repressor protein wherein any unspecified actinomycete autogenous regulatory factor acts to induce the expression of a gene placed under the control of the operator.

The specification (pages 18-42) discloses how to make and use in tobacco plant cells a gene inducing system that comprises a first genetic construct comprising a GUS reporter gene placed under the control of a nucleotide sequence (SEQ ID NO:3) obtained from the barA gene of *Streptomyces virginiae* that functions as an operator when one, two or three copies of SEQ ID NO:3 are located 3' downstream and/or 5' upstream of the TATA box of the CaMV 35S promoter in the arrangement set forth in SEQ ID NOS: 4-7 and a second genetic construct comprising a nucleotide sequence (SEQ ID NO:1) obtained from the barA gene of *Streptomyces virginiae* that encodes a polypeptide (SEQ ID NO:2) that functions as a repressor wherein the

actinomycete autogenous regulatory factor virginiae butanolide acts to induce the expression of a gene placed under the control of the operator sequence.

The specification does not disclose how to make and use in tobacco plant cells other gene inducing systems that comprise other operator sequences and other repressor polypeptides wherein other types of actinomycete autogenous regulatory factors act to induce the expression of a gene placed under the control of the operator sequence. The specification also does not disclose how to make and use in tobacco plant cells other arrangements of SEQ ID NO:3 that function as an operator when located 3' downstream and/or 5' upstream of the TATA box of the CaMV 35S promoter.

The full scope of the claimed invention is not enabled because different types of repressor proteins, operator sequences and inducer compounds cannot be predictably combined to form a gene expression inducing system that functions in plant cells since different types of repressor proteins, operator sequences and inducer compounds require different structural arrangements in order to function.

See, for example, Gatz C. et al. (Tn10-encoded tet repressor can regulate an operator-containing plant promoter. Proc Natl Acad Sci U S A. 1988 Mar;85(5):1394-7), who teach that location of tet operator sequences to flank the TATA box of the promoter of a CAT reporter gene blocks transcription of the reporter gene in tobacco plant cells in the presence of tet repressor protein, whereas the location of tet operator sequences 21 base pairs downstream of the transcription start site of a CAT reporter gene does not significantly affect transcription of the reporter gene in the presence of tet repressor protein (abstract; page 1396 Figures 2 and 3).

See also, for example, Frohberg C. et al. (Characterization of the interaction of plant transcription factors using a bacterial repressor protein. Proc Natl Acad Sci U S A. 1991 Dec 1;88(23):10470-4), who teach that binding of the tet repressor protein to a tet operator sequence blocked transcription of a CAT reporter gene in tobacco plant cells only when the tet operator sequence was inserted less than 5 bp from the TATA box, whereas in all other promoter derivatives comprising the tet operator sequence no inhibitor effect of the repressor protein was observed (abstract; page 10472 Figure 2; page 10473 Figures 3 and 4).

See additionally, for example, Wilde R.J. et al. (Control of gene expression in tobacco cells using a bacterial operator-repressor system. EMBO J. 1992 Apr;11(4):1251-9), who teach that lac protein repression of the expression of a GUS reporter gene in tobacco plant cells varied between 10% and 90% depending on the position of the lac operator in the reporter gene promoter (abstract; page 1253 Figure 4; page 1252 Figures 5 and 6).

See further, for example, Gatz C. et al. (Regulation of a modified CaMV 35S promoter by the Tn10-encoded Tet repressor in transgenic tobacco. Mol Gen Genet. 1991 Jun;227(2):229-37), who teach that the location of two tet operator sequences flanking the TATA box of a reporter gene promoter repressed reporter gene expression 5-fold in tobacco plant cells expressing a TET repressor protein, whereas location of the two tet operator sequences downstream of the TATA box repressed reporter gene expression 50-fold to 80-fold (abstract; page 233 Figure 5; page 234 Figure 6).

The specification does not provide sufficient guidance with respect to which types of repressor proteins, operator sequences and inducer compounds to use, or with respect to how to arrange the components to produce a gene expression inducing system that functions in plant

cells. Absent such guidance one skilled in the art would have to construct and test each of the myriad of combinations of repressor proteins, operator sequences and inducer compounds encompassed by the claims for their effect on gene expression in order to discriminate between those combinations that function as desired and those that do not. Such a trial and error approach to practicing the claimed invention would constitute undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 6-11, 14-17, 19-22 and 24-27, and claims dependent thereon, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in the recitation of "characters" of a repressor and operator. It is unclear which "characters" of a repressor and operator would constitute a gene expression inducing system and which would not.

Claim 1 is indefinite in the recitation of "characters of a repressor and operator both constituting a gene expression inducing system". It is unclear from the claim language exactly what constitutes the gene expression inducing system: a repressor alone and an operator alone? a repressor and an operator together? an operator character and a repressor character alone? a repressor character and an operator character together? It is also unclear whether or not "constituting" allows for the presence of additional components in the gene expression inducing system.

Claim 1 is indefinite because it is unclear what occurs "at a site of administration". Is "a gene placed under the control of the operator" at a site of administration? If so, it is unclear how this would be accomplished. Alternatively, is expression of a gene induced at a site of administration? If so, it is also unclear how this would be accomplished.

Claim 2 is indefinite in the recitation of "a genus Streptomyces". It is unclear to which genus Streptomyces the actinomycete belongs.

Claims 6 and 7 are indefinite in the recitation of "involved in". It is unclear in what way the gene expression inducing system is "involved" in the production of an antibiotic or of virginiamycin, as a gene expression inducing system may be involved in the production of an antibiotic or of virginiamycin in a number of different ways, such as by expressing the antibiotic, or by expressing an enzyme that catalyzes the biosynthesis of an antibiotic, or by expressing a protein that activates an enzyme that catalyzes the biosynthesis of an antibiotic, for example.

Claim 8 is indefinite in the recitation of "a barA gene". It is unclear which barA gene the repressor gene is.

Claims 8-10 are indefinite in the recitation of "contains". It is unclear whether the repressor gene contains anything other than the regions recited in the claims.

Claims 8-11 are indefinite in the recitation of "said repressor gene", as this limitation lacks antecedent basis in claim 1 from which claims 8-11 depend.

Claim 11 is indefinite in the recitation of "wherein a promoter for said repressor gene is a plant promoter". It is unclear what the promoter is for and/or what its relationship to the repressor gene is, since a repressor "gene" would already comprise a promoter.

Claim 8 is indefinite in the recitation of "a barA, barB or barX gene". It is unclear which barA, barB or barX gene the nucleotide sequence of said operator is derived from.

Claim 14 is indefinite in the recitation of "BARE-1, BARE-2 or BARE-3". It is unclear what sequence a nucleotide with these designations would comprise, as nucleotide sequences are understood to be comprised of four bases (A,T,G and C) in a particular linear order.

Claim 15 is indefinite in the recitation of "BARE-3". It is unclear what sequence a nucleotide with this designation would comprise, as nucleotide sequences are understood to be comprised of four bases (A,T,G and C) in a particular linear order.

Claims 16 is indefinite in the recitation of "contains". It is unclear whether the nucleotide sequence of the operator contains anything other than the regions recited in the claim.

Claim 17 is indefinite in the recitation of "wherein a promoter for said gene placed under the control of an operator is a plant promoter". It is unclear what the promoter is for and/or what its relationship to the gene is, since a "gene" would already comprise a promoter.

Claims 19-21 are indefinite in the recitation of "is disposed". It is unclear what "disposed" encompasses, as disposed has several alternative meanings. Is the operator disposed in the sense of being removed from at least one place? In the sense of being positioned in at least one place? In the sense of being transferred to or from at least one place? In the sense of at least one place being conclusive or receptive for the operator?

Claim 20 is indefinite in the recitation of "in the vicinity of a site". It is unclear where the at least one place is located, as the size of a "vicinity" would be defined differently by those skilled in the art, and the locations of "a site" 3' downstream or 5' upstream of a TATA box are not specified.

Claim 20 is indefinite in the recitation of "a TATA box". It is unclear which TATA box the of the plant promoter is the reference point for the disposition of the operator.

Claim 22 is indefinite in the recitation of "capable of". It is unclear whether the claim requires that the gene actually provide the plant with fertility.

Claim 24 is indefinite in the use of parentheses. It is unclear whether the material within the parentheses is intended to limit the claim.

Claims 25-27 are indefinite in the recitation of "cell transformed by the method according to Claim 1", as the method according to Claim 1 does not require the transformation of cells.

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia Collins whose telephone number is (571) 272-0794. The examiner can normally be reached on Monday-Friday 8:45 AM -5:15 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Cynthia Collins
Examiner
Art Unit 1638

CC

Cynthia Collins 3/7/05